REMARKS

Claims 1-58 were originally filed in this application. Claims 30-58 were withdrawn for being directed to non-elected inventions. Claims 30-58 have been canceled. Claims 4-7, 9-20, and 27-29 were withdrawn for being directed to non-elected inventions. Claims 1-3, 8, and 21-26 were examined on their merits. Claims 1-29 remain pending in this application. Claims 1-3, 8, and 21-26 remain pending for examination.

Amendments

The Abstract of the Specification has been amended in response to an objection by the Examiner. Entry of this amendment is respectfully requested.

Restriction Requirement

Applicant acknowledges that the restriction requirement has been made final. Applicant respectfully requests that, should a generic claim be found allowable, the claims withdrawn as being directed to a non-elected species be rejoined, in accordance with MPEP 809.02.

Objections to the Specification

The Examiner objected to the inclusion of the legal phrase "by this means," in the Abstract. Applicant has amended the Abstract to remove the phrase. No new subject matter was introduced. Applicant respectfully requests that this objection be withdrawn.

The Examiner noted, without objection, to the use of the trademark Sprague-Dawley (or Sprague Dawley) in the Specification. Applicant has reviewed and confirmed that in every appearance in the Specification, the trademark was capitalized and accompanied by the proper generic term, "rat." Applicant will endeavor to continue with the suggested practice.

Double Patenting

US Patent No. 6,010,846

Claims 1-2, 8, 21, 23, 24 and 26 stand rejected under the doctrine of obviousness-type double patenting over claims 1, 4-6 and 11 of US Patent No. 6,010,846. The Examiner indicated that the rejected claims "are 'anticipated' by claims 1, 4-6, and 11 of U.S. Patent No. 6,010,846 because the scope of the claims 1-2, 8, 21, 23, 24 and 26 falls entirely with the scope of claims 1, 4-6, and 11 of U.S. Patent No. 6,010,846". Office Action of 10/20/2005 at page 6.

Applicant respectfully asserts that the Examiner has not presented a sufficient basis, in accordance with MPEP 804(II)(B)(1), to establish that the rejected claims are not patentably distinct over those of US Patent No. 6,010,846. Specifically, the rejection does not make clear: A) the differences between the inventions defined in the conflicting claims and B) the reasons why a person of ordinary skill in the art would conclude that the invention defined in the rejected claims are obvious variations of the patented claims.

It is clear that the rejected claims are not 'anticipated' by claims 1, 4-6 and 11 of the '846 patent. Applicant provides below a chart comparing claims 1, 4-6 and 11 of the '846 patent with claims 1-2, 8, 21, 23, 24 and 26 of the present application:

U.S. Patent 6,010,846	Application 10/664,513
1. A method for measuring a rate of cellular proliferation or cellular destruction, comprising contacting a cell with a detectable amount of a stable isotope label which is incorporated into DNA via de novo nucleotide synthesis pathway, detecting the label in the DNA, and determining an amount of label incorporated in the DNA to measure cellular proliferation or cellular	1. A method for assessing metabolic fitness or aerobic demand of a living system, comprising: a) administering an isotopically labeled precursor molecule to the living system for a period of time sufficient for a label of said isotopically labeled precursor molecule to be incorporated into a mitochondrial molecule in said living system;

destruction. 4. The method of claim 3, wherein the DNA is hydrolyzed to deoxyribonucleosides prior to detecting the label in the DNA. 5. The method of claim 4, wherein the label is detected by mass spectrometry. 6. A method for measuring a rate of cellular proliferation or cellular destruction in a subject, comprising administering a detectable amount of a stable isotope label to the subject, which label is incorporated into DNA of the subject via de novo nucleotide synthesis pathway, detecting the label in the DNA of the subject and determining an amount of label incorporated in the DNA to measure cellular proliferation or cellular destruction. 11. The method of claim 6, wherein the subject is a human.	b) measuring an isotopic content, isotopic pattern, rate of change of isotopic content, or rate of change of isotopic pattern of said mitochondrial molecule; and c) calculating a rate of synthesis or degradation of said mitochondrial molecule to assess metabolic fitness or aerobic demand of said living system. 2. The method of claim 1, wherein the isotopically labeled precursor molecule is labeled with a stable isotope. 8. The method of claim 1, wherein the mitochondrial molecule is a deoxyribonucleic acid (DNA). 21. The method of claim 1, wherein said measuring is performed by mass spectrometry, NMR spectroscopy, or liquid scintillation counting. 23. The method of claim 1, wherein the living system is an animal. 24. The method of claim 23, wherein the animal is a mammal. 26. The method of claim 24, wherein the

	mammal is a human.

To anticipate rejected claims 1-2, 8, 21, 23, 24 and 26 of the present application, the cited claims of the '846 patent must teach every limitation of each of the pending claims. MPEP § 2131. Cited claims 1, 4-6 and 11 of the '846 patent, separately or in combination, do not teach every limitation of any of claims 1-2, 8, 21, 23, 24 or 26 of this application. Rejected claim 1 of this application is an independent claim. The remaining rejected claims, 2, 8, 21, 23, 24 and 26, are directly or indirectly dependent on at least claim 1 and therefore incorporate all of the limitations of claim 1.

The cited claims of the '846 patent are directed to "[a] method for measuring a rate of cellular proliferation or cellular destruction" through the detection of isotope label incorporation in DNA. The cited claims of the '846 patent do not teach "[a] method for assessing metabolic fitness or aerobic demand of a living system".

In the present claims, the method of assessing metabolic fitness or aerobic demand requires that the calculation of a rate of synthesis or degradation of the mitochondrial molecules be used to "assess metabolic fitness or aerobic demand" in the living system. None of the cited claims of the '846 patent teach a method for assessing metabolic fitness or aerobic demand. Without being limited by theory and with reference to paragraphs [0052] and [0053] of the specification, the relationship of mitochondria to metabolic fitness and aerobic demand is what allows for the assessment of metabolic fitness and aerobic demand, using the methods of the present application. None of the cited claims of the '846 patent teach a method that involves the use of a "mitochondrial molecule", a limitation present in all of the rejected claims of this application. Applicant accepts that DNA is a molecule which may be found in mitochondria as the cellular DNA is made up of mitochondrial DNA and nuclear DNA. However, Applicant respectfully asserts that the '846 patent is directed towards total cellular DNA while the claims of the present application are directed to mitochondrial molecules, including mitochondrial DNA, a species of the genus of total cellular DNA molecules. None of the cited claims of the '846 patent teach the use of mitochondrial DNA,

or any other mitochondrial molecule for assessment of metabolic fitness or aerobic demand. As indicated in paragraphs [0052] to [0054] of the specification, and discussed in more detail below with regards to 35 USC § 102, mitochondrial DNA exhibits properties, such as location in the cell, geometry, and mode of synthesis which differ dramatically from the majority of DNA in the cell. As such, it is a species clearly not named in claims 1, 4-6 and 11 of the '846 patent. Further, the cited claims of the '846 patent do not suggest or provide any motivation to select mitochondrial DNA from the broad genus of DNA molecules.

Claims 1, 4-6 and 11 of the '846 patent do not teach a method for assessing metabolic fitness or aerobic demand through the specific use of mitochondrial molecules and do not anticipate or render obvious claims 1-2, 8, 21, 23, 24 and 26 of the present application. Applicant respectfully requests that this ground for rejection be withdrawn.

Application No. 10/701,990

Claims 1-3, 8, and 21-26 are provisionally rejected under the doctrine of obviousness-type double patenting over claims 1, 2, 5-8, 13, 26, 29 and 31 of co-pending Application No. 10/701/990. Applicant notes that the rejection is provisional, as the conflicting claims have not been patented. The Examiner indicated that rejected claims "1-3 and 8 are 'anticipated' by claims 27 and 31 of Application No. 10/701,990 and claims 22-26 are made obvious by claims 27 and 31". Office Action of 10/20/2005 at page 6. Applicant admits to being confused as to which claims of the '990 application the Examiner intends to assert against the provisionally rejected claims, as claim 27 of the '990 applicant is omitted from the initial listing of claims raised. Applicant will address the rejection under the assumption that the Examiner intended to make the rejection based on claims 1, 2, 5-8, 13, 26, 27, 29 and 31.

Applicant respectfully disagrees with the Examiner's positions regarding both the anticipation of claims 1-3 and 8 of this application by claims 27 and 31 of the '990 application and the obviousness of claims 22-26 of this application in light of claims 27 and 31 of the '990 application.

Applicant provides below a chart comparing claims 1, 2, 5-8, 13, 26, 27, 29 and 31 of the '990 application and claims 1-3, 8 and 21-26 of the present application:

Application No. 10/701,990	Application 10/664,513 (the present application)
1. A method of determining the metabolism of one or more sugars or fatty acids in an individual, said method comprising: (a) administering one or more compositions comprising one or more ^{2}H-labeled sugars or ^{2}H-labeled fatty acids to an individual; (b) obtaining one or more bodily tissues or fluids at one or more times from said individual; and (c) detecting the incorporation of said ^{2}H from said one or more ^{2}H-labeled sugars or ^{2}H-labeled fatty acids into water to determine the metabolism of said one or more sugars or fatty acids in said individual.	1. A method for assessing metabolic fitness or aerobic demand of a living system, comprising: a) administering an isotopically labeled precursor molecule to the living system for a period of time sufficient for a label of said isotopically labeled precursor molecule to be incorporated into a mitochondrial molecule in said living system; b) measuring an isotopic content, isotopic pattern, rate of change of isotopic content, or rate of change of isotopic pattern of said mitochondrial molecule; and c) calculating a rate of synthesis or degradation of said mitochondrial molecule to assess metabolic fitness or aerobic demand of said living system.
2. The method according to claim 1, wherein said one or more compositions comprise ^{2}H-labeled glucose.	2. The method of claim 1, wherein the isotopically labeled precursor molecule is labeled with a stable isotope.
5. The method according to claim 4, wherein said one or more compositions are administered orally.	3. The method of claim 1, wherein the isotopically labeled precursor is selected from the group consisting of ^{2}H-labeled glucose, ^{13}C-labeled glucose, a ^{2}H-labeled amino acid, a ^{15}N-
6. The method according to claim 1, wherein said individual is a mammal.	

7. The method according to claim 6, wherein said mammal is chosen from humans, rodents, primates, hamsters, guinea pigs, dogs, and pigs. 8. The method according to claim 7, wherein said mammal is a human. 13. The method according to claim 1, comprising the additional step of measuring ^{2}H incorporation or incorporation ratio into one or more chemical compositions chosen from glucose, glycogen, glycerol-triglyceride, triglyceride fatty acid, proteins, and DNA. 26. The method according to claim 13, wherein said chemical composition is DNA. 27. The method according to claim 24, comprising the additional step of calculating the rate or amount of DNA synthesis. 29. The method according to claim 13, further comprising calculating the rate of or amount incorporation of ^{2}H into said one or more chemical compositions. 31. The method according to claim 1, wherein said water is detected by methods	labeled amino acid, a ^{13}C-labeled amino acid, ^{2}H-labeled acetate, ^{13}C-labeled acetate, a ^{2}H-labeled ribonucleoside, a ^{13}C-labeled ribonucleoside, a ^{15}N-labeled ribonucleoside, a ^{2}H-labeled deoxyribonucleoside, a ^{13}C-labeled deoxyribonucleoside, a ^{15}N-labeled deoxyribonucleoside, a ^{2}H-labeled fatty acid, and a ^{13}C-labeled fatty acid. 8. The method of claim 1, wherein the mitochondrial molecule is a deoxyribonucleic acid (DNA). 21. The method of claim 1, wherein said measuring is performed by mass spectrometry, NMR spectroscopy, or liquid scintillation counting. 22. The method of claim 1 wherein the isotopically labeled precursor molecule is administered orally. 23. The method of claim 1, wherein the living system is an animal. 24. The method of claim 23, wherein the animal is a mammal. 25. The method of claim 24, wherein the

chosen from gas chromatography/mass spectrometry, liquid chromatography-mass spectrometry, gas chromatography-pyrolysis-isotope ratio/mass spectrometry, gas chromatography-combustion-isotope ratio/mass spectrometry, cycloidal mass spectrometry, Fourier-transform-isotope ratio (IR)-spectroscopy, near IR laser spectroscopy, and isotope ratio mass spectrometry.	mammal is a rodent. 26. The method of claim 24, wherein the mammal is a human.

Cited claims 1, 2, 5-8, 13, 26, 27, 29 and 31 of the '990 application, separately or in combination, do not teach every limitation of any of claims 1-3, 8 or 21-26 of this application. Rejected claim 1 of this application is an independent claim. The remaining rejected claims of this application, 2, 3, 8 and 21-26 are directly or indirectly dependent on at least claim 1 and therefore incorporate all of the limitations of claim 1.

The cited claims of the '990 application are directed to "[a] method of determining the metabolism of one or more sugars or fatty acids in an individual" through the detection of isotope label incorporation in DNA. The cited claims of the '846 patent do not teach "[a] method for assessing metabolic fitness or aerobic demand of a living system". The rejected claims teach a method for determining metabolic fitness or aerobic demand. The specification in the present application, at paragraphs [0030] and [0032], define "metabolic fitness" and "aerobic demand" as "the capacity for oxidative metabolism or aerobic activity of a living system" and "the oxidative needs imposed on a cell, tissue, or organism in vivo", respectively. "Oxidative metabolism" is itself defined in paragraph [0049] of the specification as "the sum total of all energy-yielding biochemical transformations of fuels...that ultimately require the involvement of molecular oxygen interacting with the molecular phosphorylation apparatus". While the metabolism of sugars or fatty acids may play a role in metabolic fitness or aerobic demand, clearly metabolic fitness and aerobic demand encompass a total oxidative metabolism which is both broader, in the sense that it involves fuels

beyond sugars and fatty acids, and narrower than the metabolism of sugars or fatty acids, which may also involve anaerobic metabolism of the sugars or fatty acids.

Further, the cited claims of the '990 application teach a method for determining the metabolism of one or more sugars or fatty acids through the detection of isotope label into H_2O. The claims of the present application are directed to a method of assessing metabolic fitness or aerobic demand by detecting isotope label incorporation into mitochondrial molecules. Mitochondrial molecules do not include free H_2O molecules. Accordingly, the cited claims of the '990 application do not teach a method involving the detection of isotope label into mitochondrial molecules.

Nor would it be obvious to one skilled in the art to adapt the methods of the '990 application to a method for assessing metabolic fitness or aerobic demand involving the detection of isotope label into mitochondrial molecules. Accordingly, Applicant respectfully disagrees that the rejected claims are not patentably distinct over those of co-pending application 10/701,990 and requests that this ground for rejection be withdrawn.

Claim Rejections - 35 USC § 102

US Patent No. 5,910,403

Claims 1-3, 8 and 21-26 stand rejected under 35 USC § 102(b) as being anticipated by US Patent No. 5,910,403, listing Hellerstein as the inventor ("the '403 patent").

Applicant respectfully disagrees. To anticipate a claim, a cited reference must teach every element of the claim. MPEP § 2131. The '403 patent does not teach "[a] method for assessing metabolic fitness or aerobic demand of a living system" through the detection of isotope label incorporation into a mitochondrial molecule.

The '403 patent teaches methods for determining cellular proliferation through the detection of isotope label into cellular DNA. However, the '403 patent does not teach the determination of metabolic fitness or aerobic demand of a living system nor does the '403 patent specifically teach the use of mitochondrial molecules such as mitochondrial DNA.

A determination of cellular proliferation rate differs markedly from a determination of the metabolic fitness or aerobic demand of a living system, such as a cell. As mentioned above, "metabolic fitness" is "the capacity for oxidative metabolism or aerobic activity of a living system". In the case of a cell, this characteristic is separate from the cellular proliferation rate, as one is an indication of capacity for oxidative metabolism while the other is a measure of the rate at which cells are replicating. While the '403 does teach a method for determining the rate of DNA synthesis as an indication of cellular proliferation rate, the '403 patent does not recognize nor does it teach the assessment of metabolic fitness from the calculated synthesis or degradation of mitochondrial molecules. The importance of this teaching is highlighted in paragraphs [0052] and [0053] of the specification, which discusses the relevance of mitochondrial mass in aerobic metabolism. The '403 patent does not teach or recognize the relationship between mitochondrial molecules, including mitochondrial DNA, and metabolic fitness or aerobic demand and therefore does not teach how to assess metabolic fitness or aerobic demand based on a determination of the synthesis or degradation rate of mitochondrial molecules.

Further, while the '403 patent teaches the use of cellular DNA, it does not specifically teach the use of mitochondrial DNA, which is a specific mitochondrial molecule as claimed in the present application. Without being limited by theory, the specification of this application teaches, mitochondrial DNA differs markedly from generic DNA. For example mitochondrial mass increases in response to aerobic exercise and decreases in response to deconditioning. Paragraph [0053] of the specification. Further, mitochondrial DNA is separate and distinct from the remainder of eukaryotic DNA (i.e. nuclear DNA) in its location, geometry, mode of synthesis, etc. Paragraph [0054] of the specification. Importantly, mitochondrial DNA replication is linked to mitochondrial RNA synthesis. As the specification teaches, this results in coordinate induction of increased mitochondrial DNA synthesis with increased need for mitochondrial RNA. Paragraph [0054] of the

specification. Given the mitochondria's role in oxidative metabolism and aerobic activity, the use of mitochondrial molecules, specifically, is a unique feature of the present application, which is not disclosed in the '403 patent which only teaches the use of total cellular DNA. *Cf.* paragraph [0052] of the specification. Applicant respectfully requests that this ground for rejection be withdrawn, as the '403 patent does not teach every limitation of the pending claims.

US Patent No. 6,010,846

Claims 1, 2, 8, 21, 23, 24 and 26 stand rejected under 35 USC § 102(b) as being anticipated by US Patent No. 6,010,846, listing Hellerstein as the inventor ("the '846 patent").

Applicant respectfully disagrees and reiterates the argument presented above with respect to double patenting in light of the '846 patent and anticipation in light of the '403 patent. As with the above rejection, the '846 patent does not teach every element of any of the claims rejected. The '846 patent does not teach "[a] method for assessing metabolic fitness or aerobic demand of a living system" through the detection of isotope label incorporation into a mitochondrial molecule.

The '846 patent teaches methods for determining cellular proliferation or destruction. However, for the reasons stated above, metabolic fitness and/or aerobic demand of a living system, such as a cell, differs markedly from cellular proliferation or destruction rates. As with the '403 patent, the '846 patent does not recognize the relationship between mitochondrial molecules and oxidative metabolism and therefore does not disclose a method of assessing metabolic fitness or aerobic demand.

Additionally, the '846 patent does not teach the specific use of mitochondrial molecules. The reference does teach a method for determining the synthesis or degradation of generic DNA. However, as in the '403 patent, the generic teaching is insufficient. Applicant again directs the Examiner's attention to the passages cited above, regarding the unique properties of mitochondrial DNA. Accordingly, the '846 patent does not teach the use of mitochondrial DNA, specifically, which is critical to the claims of the present application.

The '846 patent does not anticipate the claims of this application as the reference does not teach every element of any of the rejected claims. Applicant requests that this ground for rejection be withdrawn.

Applicant also notes that the Examiner states, in the discussion of the '846 patent, that "the invention as a whole is *prima facie* obvious to one with ordinary skill in the art." Respectfully, such is not the standard for an anticipation rejection, which requires that the cited reference teach every element of the claim. Rather, it appears that the Examiner intended to make an obviousness rejection. Even assuming that the rejections were made based on 35 USC § 103(b), claims 1, 2, 8, 21, 23, 24 and 26 are not *prima facie* obvious, in light of the '846 patent. The differences in mitochondrial DNA disclosed in paragraphs [0053] and [0054] along with its use in determining metabolic fitness render the claims of this application nonobvious over the '846 patent and therefore not subject to a rejection under 35 USC § 103(b). One skilled in the art would have no motivation to modify the methods disclosed in the '846 patent for use in an assessment of metabolic fitness nor would one of skill be motivated to use mitochondrial molecules with the methods disclosed.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. **416272003700**.

sf-2084122

However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: February 21, 2006

Respectfully submitted,

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sf-2084122